## REMARKS

Claims 1 and 3-15 are pending in the current application. Claim 10 is canceled. New claims 21-23 have been added. Support for the new claims can be found in the specification, for example, in Examples 2 and 3 on pages 21-22. All rejections as set forth in the Office Action of March 9, 2006 are addressed below.

## I. REJECTION UNDER 35 USC §101

The Examiner has rejected claim 10 as allegedly lacking patentable utility under 35 USC §101. The Applicants submit the Examiner has improperly interpreted the law and the Patent Office's guidelines in rejecting the claims under 35 USC §101. However, for business reasons and for the purpose of expediting the patent application process in a manner consistent with the PTO's Patent Business Goals (PBG),[1] and without waiving the right to prosecute the canceled claim (or a similar claim) in the future, claim 10 has been canceled. It should be noted, however, that claim 1 still encompasses variants of a nucleotide cyclase, and the cancellation of claim 10 does not alter this.

As such, the Applicants respectfully request that the rejection be withdrawn.

## II. REJECTION OF CLAIMS UNDER 35 USC §102(a)

The Examiner has rejected Claims 1, 5-6 and 14 under 35 USC §102(a) as allegedly being anticipated by Gille A & R Seifert, 2003, Journal of Biological Chemistry 278(15):12672-12679 (hereafter Gille). The Applicants assume that the Examiner meant to refer to the aforementioned journal citation, as an equivalent Gille & Seifert paper is not found at the same volume and page numbers in the Journal of Biological Sciences as referenced by the Examiner. The Applicants respectfully disagree with the Examiner's rejection.

To anticipate a claim, the reference must teach each and every element of the claim as required by MPEP §2131. Gille teaches the functional effects of a variety of

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[1] 65 Fed. Reg. 54603 (Sept., 8, 2000).

guanosine nucleotide analogs on G-protein mediated signaling in insect cells via the adenylyl cyclase enzyme using radioactive assays. The Examiner states that the Applicants previous argument was found unpersuasive as Figure 5 shows assay reactions using test compounds, wherein the initial time point is equivalent to an assay condition where the test compound was not added (absence of a test compound). The Applicants respectfully suggest that the Examiner has not considered the full scope of the Applicants previous argument as stated on pages 6-7 of the Amendment and Response to Final Office Action dated February 8, 2006. The Applicants argument with respect to this rejection states "...Gille does not teach the claim elements of measuring the level of fluorescence of said fluorescently labeled substrate or comparing said level of fluorescence of said fluorescently labeled substrate in the presence of said test compound to the level of said fluorescence in the absence of the test compound..." (emphasis added). Gille does not teach the use of fluorescence as a method to compare the ability of a test compound to modulate nucleotide cyclase activity as defined by the present claim elements. The AC assay of Gille, as used to create Figure 5, is one of radioactive measurement (page 12673-12674 "AC Assay"), not measuring the level of fluorescence of a fluorescently labeled substrate in the presence or absence of a test compound. Therefore, Gille does not anticipate each and every element of claims 1, 5-6, and 14 as required by MPEP §2131 because Gille does not teach the use of fluorescence to measure the ability of a test compound to modulate nucleotide cyclase activity. As such, the Applicants request that the rejection be withdrawn.

## III. REJECTION OF CLAIMS UNDER 35 USC §103

The Examiner has rejected claims 1-9 and 11-15 under 35 USC §103(a) for allegedly being unpatentable over Herr et al. (US Patent Application 2002/0064849 A1, hereafter Herr) in view of Gille & Seifert (2003, Life Sciences 74:271-279, hereafter Gille). The Applicants respectfully disagree with the rejection and submit that the Examiner has failed to provide a *prima facie* case of obviousness over Herr in view of Gille as required by MPEP §2143 for claims 1, 3-9 and 11-15. There are three criteria that must be met to provide *prima facie* obviousness. The first of these criteria is a suggestion or motivation in the reference(s), or the knowledge generally available to one

of ordinary skill in the art, to modify the reference or combine reference teachings. The second criterion is that the prior art must teach or suggest a reasonable expectation of success. The third criterion is that the prior art reference(s) must teach or suggest all the claim limitations.

The Applicants submit that the combination of references cited by the Examiner do not teach all of the elements as required for rejection under 35 U.S.C. §103(a). Herr teaches the cloning and characterization of an adenylyl cyclase enzyme utilizing radioactively labeled substrates and radioactive assays for monitoring adenylyl cyclase activity. Herr does not teach the use of fluorescence measurement in comparing the level of fluorescence of a fluorescently labeled substrate in the presence of a test compound to the level of fluorescence in the absence of the test compound in the presence of a nucleotide cyclase. The Examiner states that the Applicants previous argument was found unpersuasive as Gille shows assay reactions with test compounds, wherein the initial time point is equivalent to an assay condition where the test compound was not added. The Applicants respectfully suggest that the Examiner has not considered the full scope of the Applicants previous argument. The presence or absence of a test compound is only one part of the argument, whereas comparing the level of fluorescence in the presence or absence of a test compound is an equally important component of the claim (page 7, Amendment and Response to Final Office Action dated February 8, 2006). Gille (page 273-274) states that the MANT nucleotides prevented them from developing a fluorescent assay, as the fluorescent MANT group significantly decreased the GPCRs affinity for those MANT nucleotides, thereby rendered them unsuitable for fluorescent studies in cell membranes. The AC assay used by Gille was in fact a radioactivity assay, the very one used in Gille A & R Seifert, 2003, Journal of Biological Chemistry 278(15):12672-12679, as previously described. The Applicants assert that neither Gille nor Herr use, or suggest the use of, fluorescence measurement to compare levels of a fluorescently labeled substrate in the presence or absence of a test compound. In fact, Herr is moot to the use of fluorescence, indeed only describing and using radioactive nucleotides and associated assays for measurement of adenylyl cyclase activity (for example, see page 5 paragraph 0059 and page 7, Example 3).

There is no suggestion or motivation that one skilled in the art would combine these two references to practice all the limitations of the present claim. There is additionally no suggestion that one skilled in the art would have any success in creating a method of the present claims by combining Herr, a reference which teaches only radioactive substrates and assays, with Gille who admittedly had no success is creating a fluorescent assay for measurement of fluorescently labeled substrates of adenylyl cyclase.

As such, the Applicants submit that the Examiner has not demonstrated a *prima facie* case of obviousness and respectfully requests that the rejection be withdrawn.

The Examiner has rejected Claims 1-7 and 11-15 under 35 USC §103(a) as allegedly being unpatentable over Herr in view of Rossomando et al. (1981, Proc. Natl. Acad. Sci 78(4):2278-2282, hereafter Rossomando), further in view of McEwan et al. (2001, Anal. Biochem. 291:109-117, hereafter McEwan). The Applicants respectfully disagree and submit that the Examiner has failed to provide a *prima facie* case of obviousness over Herr in view of Rossomando, further in view of McEwan as required by MPEP §2143 for claims 1, 3-7 and 11-15.

The teachings of Herr have been previously described. Rossomando teaches that a fluorescent ATP analog, FoTP, can be utilized as a substrate by adenylate cyclase. Rossomando further teaches that the fluorescent cyclized product (cFoMP) is purified from the other reaction products via HPLC prior to detection by fluorometry (page 2279, Experimental Procedures). Therefore, Rossomando only teaches fluorometric assay of purified cyclic FoMP.

McEwen teaches the use of various fluorescently (BODIPY) labeled guanine nucleotide molecules as probes to study the binding kinetics between the guanine nucleotide ligand and its G-protein receptor. McEwen teaches receptor-ligand binding, not the use of a fluorescently labeled substrate in a method to define test compounds that modulate nucleotide cyclase enzyme kinetics. The Applicants assert that McEwen does not teach, or suggest anywhere, that his labeled nucleotides can be used in enzymatic assays as a fluorescent substrate and further used to screen for test compounds that modulate nucleotide cyclase activity.

Herr does not teach fluorescent substrates and assays as previously described. Rossomando only teaches the detection of a purified nucleotide cyclase and does not teach the detection of fluorescently labeled substrates to test for compounds that could modulate nucleotide cyclase activity. McEwen does not teach the use of fluorescent nucleotides as a substrate for nucleotide cyclases, nor the use of such substrates to test for compounds that could modulate nucleotide cyclase activity. Neither Herr nor Rossomando nor McEwan, alone or in combination, teach all of the elements of the claims as required for rejection under 35 USC §103 (a) and respectfully request that the rejection be withdrawn.

The Examiner has rejected claims 1-9 and 12-15 under 35 USC §103(a) as allegedly being unpatentable over Remmers et al. (1994, J. Biol. Chem. 269(19):13771-13778, hereafter Remmers) in view of Holtwick et al. (2002, Proc. Natl. Acad. Sci. 99(10):7142-7147, hereafter Holtwick). The Applicants respectfully disagree with the rejection and submit that the Examiner has failed to provide a *prima facie* case of obviousness over Remmers in view of Holtwick as required by MPEP §2143 for claims 1, 3-9 and 12-15.

Remmers teaches the use of fluorescently labeled nucleotide analogs as probes to study the binding kinetics of the nucleotide ligands with their G-protein receptors. Remmers does not teach the use of fluorescently labeled nucleotides as a substrate for a nucleotide cyclase enzyme, nor does it suggest the described ligands can be used for such a purpose. Remmers teaches the use of mastoparan as an agonist for G-protein coupled binding, however there is no suggestion that mastoparan could be a potential modifier of nucleotide cyclase enzyme activity. Indeed, nucleotide cyclase activity is not dealt with in the paper.

Holtwick teaches that atrial natriuretic peptide (ANP) is important in the regulation and maintenance of arterial blood pressure, and states that ANP is an activator of guanylyl cyclase-A (GC-A). Holtwick further teaches the creation of smooth muscle GC-A knock-out mice to study the contribution of GC-A on ANP related blood pressure. Holtwick does not teach or suggest a method of using fluorescence as a means of screening test compounds for their ability to modulate nucleotide cyclase activity on its fluorescently labeled substrate. Indeed, the only assay used to measure GC-A activity in

Holtwick is a radioimmunoassay for cGMP enzymatic end product (page 7143-4, Materials and Methods). As described by the Examiner, Holtwick does state that GC-A might be important in other physiological processes (page 7147, second column) as well as playing a role in cardiovascular disease via interaction with ANP. The Applicants do not dispute these findings, as there is a body of evidence that exists as referenced by the author that points to those relevant studies, as well as his own findings. These statements further justify why nucleotide cyclases are important enzymes for future study and furnish utility for why it is important to find compounds that modulate cyclases; their importance in disease processes make them targets for drug discovery and as potential treatment targets. However, this admission by Holtwick does not provide one skilled in the art any insight into practicing the present invention. A skilled artisan would have no motivation to combine, nor any suggestion of success in applying, the nucleotide analog of Remmers which is used as a probe in studying G-protein binding kinetics, with the mice of Holtwick which have been engineered to contain no nucleotide cyclase in its smooth muscle or those used as controls, to screen for test compounds which might modulate a nucleotide cyclase.

As such, the Applicants submit that neither Remmers nor Holtwick, alone or in combination, teach all of the elements of the claims as required for rejection under 35 USC §103 (a) and respectfully request that the rejection be withdrawn.

## CONCLUSION

All grounds of rejection of the Office Action of March 9, 2006 have been addressed and reconsideration of the application is respectfully requested. It is respectfully submitted that the Claims should be allowed. Should the Examiner have any questions, or if a telephone conference would aid in the prosecution of the present application, Applicants encourage the Examiner to call the undersigned collect at 608-218-6900

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